OSTEOGENESIS IMPERFECTA: THE AUDIOLOGICAL PHENOTYPE LACKS CORRELATION TO THE GENOTYPE

Freya Swinnen[1], Paul Coucke[2], Anne De Paepe[2], Sofie Symoens[2], Fransiska Malfait[2], Filomena Gentile[3], Luca Sangiorgi[3], Patrizia D'Eufemia[4], Ton Garretsen[5], Cor Crermers[6], Ingeborg Dhooge[1], Els De Leenheer[1]

[1]Otorhinolaryngology, Ghent University Hospital, Belgium; [2]Center for Medical Genetics, Ghent University Hospital, Belgium; [3]Medical genetics and Rare Orthopaedic Diseases, Rizzoli Orthopaedic Institute, Bologna, Italia; [4]Department of Pediatrics, La Sapienza University of Rome, Italy; [5]Department of Otorhinolaryngology, Medical Centre Alkmaar, The Netherlands; [6]Otorhinolaryngology, Radboud University Nijmegen Medical Center, The Netherlands

Background

- 50% of the patients with osteogenesis imperfecta (OI) demonstrate hearing loss
- Onset: 2nd to 4th decade of life
- Types of hearing loss reported in OI:

Conductive loss	• Pathological condition in the outer or middle ear • In OI caused by stapes footplate fixation or atrophic/fractured ossicles.
Sensorineural loss	• Pathological condition in the inner ear (cochlea) • In OI due to microfractures of the cochlea, atrophy of the cochlear hair cells, atrophy of the stria vascularis, perilymphe hemorrhage
Mixed hearing loss	• Combination of conductive and sensorineural pathology • Most common type of hearing loss in OI.

- Research aims:
  - to unravel the characteristics of the hearing loss and their interindividual variability
  - to investigate associations between the occurrence and characteristics of the hearing loss and the underlying mutations causing OI

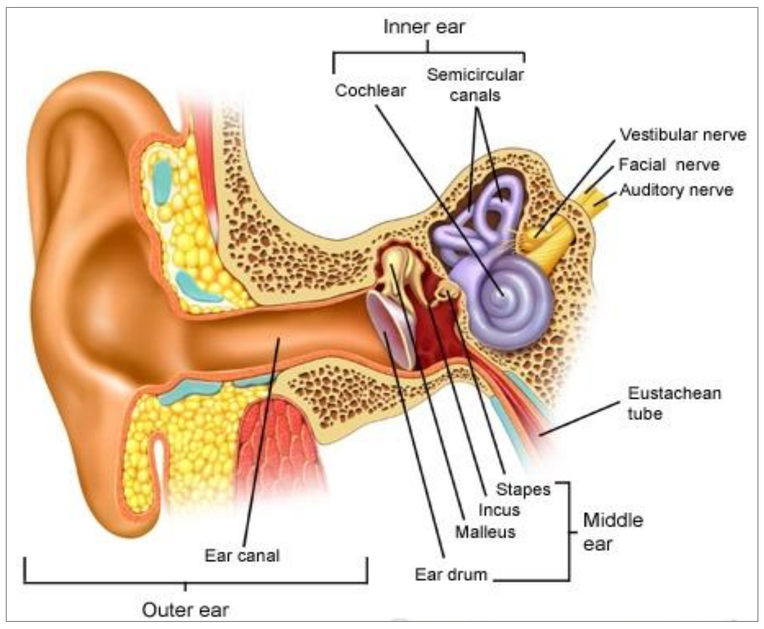

Figure 1. Cross-section of the ear, in which we distinguish the outer, middle and inner ear.

Methods

- 89 OI probands + 95 affected relatives = 184 OI patients (type I:154; type III:4; type IV:26), aged 3-89 years
  - 43 Belgian
  - 25 Dutch
  - 21 Italian

Mutation screening/analysis:
- Mutated gene (COL1A1 or COL1A2)
- Type I collagen defect (quantitative or qualitative)
- Location of the mutation (C-terminal propeptide, triple helix, N-terminal propeptide)

Audiological evaluation:
- Hearing loss type (conductive, mixed or sensorineural)
- Severity
- Symmetry

Results

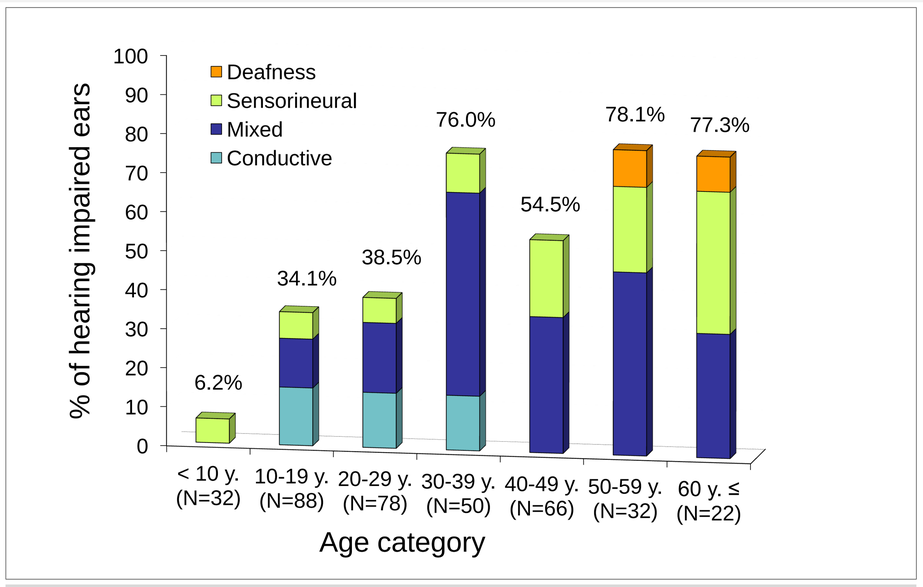

Figure 2. Prevalence and type of hearing loss as a function of age in a total number of 368 ears

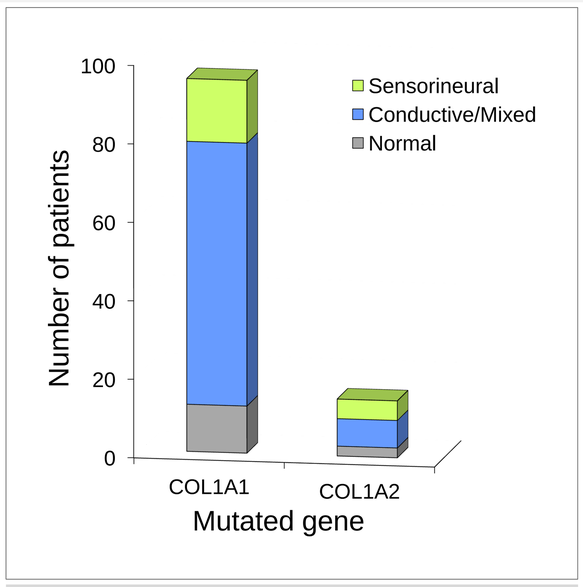

Figure 3. Prevalence and type of hearing loss as a function of mutated gene

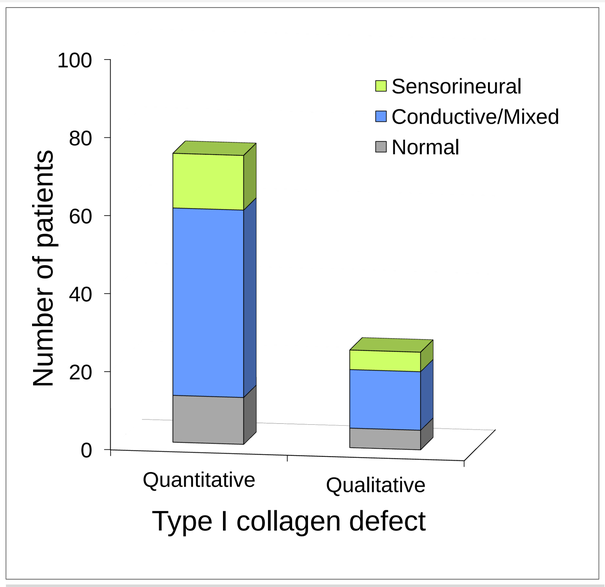

Figure 4. Prevalence and type of hearing loss as a function type I collagen defect

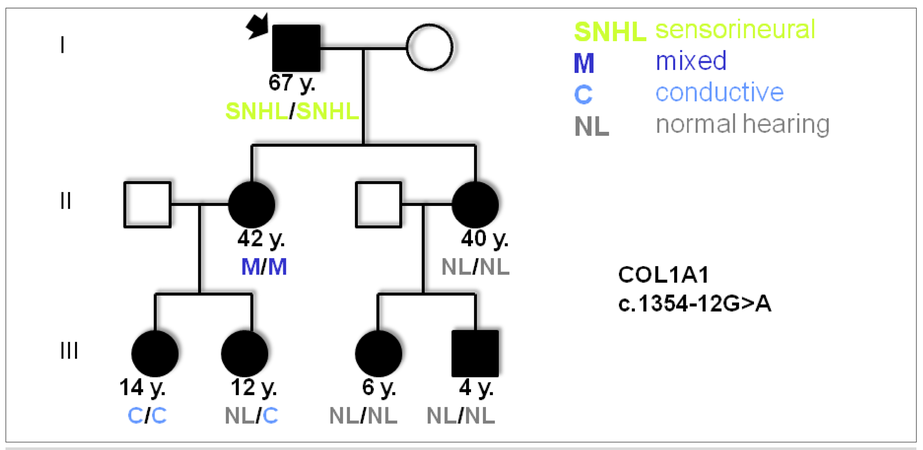

Figure 5. Intrafamilial variability in audiological phenotype

- Prevalence: 48.4% of OI ears; ↑ in the older age groups (figure 2)
- Hearing loss type: mixed hearing loss (27.5%); sensorineural hearing (12.5%); conductive (8.4%)
- Severity varied from mild hearing loss to deafness.
- No association between mutated gene or the nature of the type I collagen defect and the occurrence or type of hearing loss (figures 3 and 4).
- Affected relatives with an identical mutation in *COL1A1* or *COL1A2* differed in audiological phenotype (figure 5).

Discussion and Conclusion

- Prevalence of hearing loss in the overall OI population amounts to about 50% and rises with increasing age.
- The predominant type of hearing loss is a bilateral, symmetric and progressive mixed hearing loss with conductive onset.
- No associations between development and type of hearing loss and a mutation in *COL1A1* or *COL1A2*, the quantitatively or qualitatively disturbed type I collagen synthesis or the location of the mutation with respect to the triple helical domain.
- Inter- and intrafamilial variability in the development and characteristics of OI-related hearing loss.
- Additional modifications in other genes are assumed to be responsible for the expression of hearing loss in OI.

Freya.Swinnen@UGent.be
De Pintelaan 185, 1P1
9000 Ghent
Belgium